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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/079,640	05/15/1998	HENRY DANIELL	922.6588P	8567

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PHILADELPHIA, PA 19103

EXAMINER
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FOX, DAVID T

ART UNIT	PAPER NUMBER
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1638

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/079,640

Applicant(s)

DANIELL, HENRY

Examiner

David T. Fox

Art Unit

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2003 and 24 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1,3-96,100-191,193-196 and 200-214 is/are pending in the application.
- 4a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.
- 5) ☒ Claim(s) 4-84,86-96,107,118,119,122,168,169,172-176,189,194 and 195 is/are allowed.
- 6) ☒ Claim(s) 3,171,190,191,193,196 and 214 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,85,100-106,108-117,120,121,123-167,170,177-188 and 200-213.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The amendments of 15 September 2003 have been entered. The Supplemental Response of 24 September 2003 which clarified some of the rebuttal text in the amendment of 15 September 2003 has also been considered. The references submitted with both amendments have been reviewed.

The amendments of 15 September 2003 and accompanying arguments have overcome the outstanding claim errors, the obviousness-type double patenting rejection, the outstanding new matter rejection, the outstanding indefiniteness rejections, and the art rejections of claim 192.

The application should be reviewed for errors. Errors appear, for example, in claims 193 and 214 as presented in the amendment of 15 September 2003. Claim 193, which is designated as "Previously amended". However, line 1 of claim 193 recites "Anu" which indicates a concurrent amendment. Furthermore, "An universal" in line 1 is grammatically incorrect. Errors also appear in claim 214, line 6, where "whrein" should be replaced with -- wherein-- --; and in line 13, where the comma after "genome" has a dash directly above it.

Claims 196 and 214 (amended) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 196 is indefinite in its recitation in line 7 of "the coding sequences" which lacks antecedent basis in the claim, since there is only one coding sequence recited.

Claim 214 is indefinite in its recitation in line 12 of "said homologous recombination" which lacks antecedent basis in the amended claim.

Claims 3, 171, 190-191, 196, and 214 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 190-191, 196 and 214 as amended recite NEW MATTER as set forth below. Dependent claims 3 and 171 are also included in the rejection. Applicant is notified that amendment of the claims to address the NEW MATTER issue will result in the reinstatement of the obviousness-type double patenting rejection over the claims of Daniell et al (U.S. Patent 5,932,479).

Claims 190-191, and 196 recite "control sequences positioned upstream from either of the 5' end or downstream of the 3' end, but not both" (see, e.g., claim 190, lines 4-5). Claims 190-191, 196 and 214 have been amended to indicate that the transcriptionally active intergenic spacer region is not conserved (see, e.g., claim 190, penultimate line). Claim 191 has been amended to recite that a promoter is present but another type of 5' control sequence might not be present (see, e.g., lines 5-6). Claim 214 has been amended to recite that no promoter is present but another type of 5' regulatory sequence might be present (see, e.g., lines 4-6). There is no basis in the specification for any of this language or these concepts. Accordingly, the claims are directed to NEW MATTER.

Applicant's arguments filed 15 September 2003 and 24 September 2003 have been fully considered but they are not persuasive. Applicant urges that Figures 2A-2B, 3A-3B, 7B, 7D, 8 and 25 of the instant specification; Examples 1, 10-11 and 16 of the instant specification; and Figure 2B of Ruiz et al (2003) provide basis for the amendments.

The Examiner maintains that only Figures 7D and 8 show plastid transformation constructs with no 3' regulatory region after the coding sequences. All of the Figures and Examples teach constructs with a heterologous promoter ligated to two tandemly linked polycistronic coding regions. All Figures other than Figures 7D and 8 additionally teach the presence of a 3' regulatory region at the end of the polycistronic coding region. Figure 25 presents the results of plant transformation with the plasmid of Figure 2A.

No Figures or Examples teach any construct without a promoter or without another type of 5' regulatory region, as claimed. See, e.g., Figure 2A, which teaches the Prn promoter (5' regulatory region) ligated to an aadA marker gene, which marker gene is directly ligated to an EPSPS gene of interest, which gene of interest is directly ligated to a psbA 3' regulatory region. The Prn promoter and psbA 3' regulatory region found on the construct directly regulate the transcription of both the aadA gene and the EPSPS gene, *not* a native promoter or 3' regulatory region found in some putative "transcriptionally active region" of the genome of the chloroplast into which the construct is inserted. It is well known in the art that such polycistronic transcription systems are

common in chloroplasts (see, e.g., Sugita et al cited by Applicant, page 317, column 2 and page 318, column 1).

Similarly, Example 1 teaches the use of the polycistronic construct of Figure 2B which contains its own promoter and 3' regulatory region (see, e.g., page 41 of the specification, line 23). Example 10 teaches the use of the polycistronic constructs of Figures 3A and 3B, each of which contain its own promoter and 3' regulatory region (see, e.g., page 52 of the specification, lines 25-26). Example 11 also teaches the use of the polycistronic construct of Figure 2A which contains its own promoter and 3' regulatory region (see, e.g., page 57, lines 4-6). Only Example 16 demonstrates the use of a genetic construct with no 3' regulatory region, that of Figure 8A (see, e.g., page 64 of the specification, lines 27-29). However, that example does not describe the use of any genetic construct with no promoter or no 5' regulatory region, or both.

Regarding Ruiz et al, the Examiner notes that the reference teaches the use of the same intergenic spacer region as that exemplified by Applicant, namely the trnI/trnA spacer region, and transformation therewith by a construct without a 3' regulatory region but with a Pr<sub>rrn</sub> promoter (see, e.g., page 2, column 2, top paragraph). Thus, Ruiz et al do not provide any additional information not provided by the instant specification.

Claims 3, 171, 190-191 and 196 remain, and newly amended claim 214 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the intergenic spacer 2 region between the trnA and trnI genes of the chloroplast genome of higher plants, does not reasonably provide enablement for claims broadly drawn to the use of any transcriptionally active spacer

region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, as stated on page 4 of the last Office action for claims 3, 171, 190-192 and 196-199.

Claims 190-191, 193 and 196 remain, and newly amended claim 214 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the intergenic spacer 2 region between the trnA and trnI genes of the chloroplast genome of higher plants for the homologous recombination-mediated insertion of heterologous DNA into the intergenic spacer 2 region of higher plants, does not reasonably provide enablement for the insertion of heterologous DNA into any "transcriptionally active" or "conserved" intergenic spacer region of the chloroplast genome of a multitude of higher plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, as stated in the last Office action on pages 4-5 for claims 190-193 and 196-199.

Applicant's arguments filed 15 September 2003 and 24 September 2003 have been fully considered but they are not persuasive.

Applicant urges that the enablement rejections are improper, given the demonstration by Sugita et al in Table 2 on page 317 of over 60 intergenic spacer regions in the plastid genome, the demonstration by Rainer et al of such regions in the corn chloroplast genome and others, the demonstration by Ruf et al of genetic insertion into another spacer region on page 874, and Table 2 of the Daniell et al (2003)

manuscript which teaches the existence of spacer regions into which foreign genes have been inserted.

The Examiner maintains that none of the cited references teach or provide guidance for the claimed subject matter, i.e. intergenic spacer regions which are either transcriptionally active (claims 3, 171, 190-191, 196 and 214) or conserved (claim 193). Sugita et al in Table 2 merely provide a list of polycistronic transcription units, i.e. directly linked coding sequences encoding different proteins, which linked coding sequences are naturally regulated by a single upstream 5' promoter and a single downstream 3' untranslated region. No information is given regarding *any* intergenic spacer region, either conserved or transcriptionally active or otherwise.

Maier et al merely provide a map of the maize chloroplast genome and also provide a comparison of the size of the chloroplast genomes of maize and other plant species. The authors also discuss regions of genetic diversity and mutation within the genome. No guidance or information is provided regarding any particular intergenic spacer region, or its transcriptional activity. Regarding conservation of intergenic spacer regions as claimed in claim 193, Maier et al actually teach the divergence of said spacer regions, in the lack of proximity between the *rbcl* and *accD* chloroplast genes in maize, in contrast to dicotyledonous plants (see, e.g., page 619, Figure 2B).

Ruf et al in Figures 1B-1C teach a genetic construct comprising a 5' regulatory region (the *Prn* promoter), an *aadA* coding sequence, and a 3' regulatory region (the *psbA* transcription terminator). Since the genetic construct has its own 5' and 3' regulatory regions, its expression cannot be due to any native 5' or 3' regulatory region

in any putative transcriptionally active spacer region. Ruf et al is also silent with regard to the conservation of any intergenic spacer region.

Daniell et al (2003) teach the insertions of various genetic constructs into several intergenic spacer regions of the chloroplast genome (see Tables 1 and 2). Almost all of the insertions took place in Applicant's single exemplified trnI/trnA spacer region. In all of the insertions, a genetic construct with both 5' regulatory elements and 3' regulatory elements was used (see, e.g., Table 1, row 1, where a Prn promoter, 5' regulatory element from the rbcL gene, and a 3' regulatory element of the Trps16 gene was used). See also page 3 of the manuscript, bottom paragraph; and page 8, first full paragraph; which disclose the need for a promoter as well as 5' and 3' regulatory elements in the genetic construct. Thus, transcription of each of the coding sequences in Tables 1 and 2 is dependent upon the 5' and 3' regulatory elements directly ligated thereto in the genetic construct. No putative 5' or 3' regulatory elements or promoters which are native to any putative transcriptionally active intergenic spacer region are needed. Although Applicant's specification has taught that the trnI/trnA spacer region is in fact transcriptionally active, Daniell et al (2003) provide no evidence that any other intergenic region possesses this property, let alone those listed in Tables 1 and 2.

Note also Applicant's admission on page 5 of the Supplemental Response of 24 September 2003, first two paragraphs, that transcriptionally silent intergenic spacer regions also exist in the chloroplast genome. None of the cited references, or Applicant's specification, provide any evidence that any intergenic spacer region other than the exemplified trnI/trnA region is in fact transcriptionally active.

Furthermore, neither the cited references nor Applicant's specification provide any guidance regarding the identification or isolation of any transcriptionally active or non-conserved intergenic spacer region. Page 27 of the specification, line 12 through page 28 of the specification, line 9 only provide general guidance regarding the general protocol needed to isolate *conserved* intergenic spacer regions, as claimed only in claim 193. However, no specific information regarding specific conserved sequences used to probe for such conserved regions is provided; and no information of any kind is provided for identifying any other transcriptionally active regions, via sequence conservation or any other means.

Additionally, it is noted that amended claims 191 and 196 no longer indicate that the flanking DNA in the genetic construct is of chloroplast origin, since the deleted material states that the flanking DNA "is complementary to chloroplast sequences of the target plant" (see, e.g., claim 191, lines 8-10). The flanking DNA is used to effect homologous recombination with the chloroplast genome, thus allowing integration of the genetic construct into the intergenic spacer region. Neither the specification nor any cited reference provides guidance for obtaining homologous recombination between non-chloroplast DNA (as newly claimed in amended claims 191 and 196) and chloroplast DNA present in the intergenic spacer region of the chloroplast genome. Given the requirement of sequence identity for homologous recombination to occur, newly amended claims 191 and 196 are not enabled for this aspect as well.

Claims 3, 171, 190-191, 193 and 196 remain, and newly amended claim 214 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written

description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as stated on pages 5-7 of the last Office action for claims 3, 171, 190-193 and 196-199.

Applicant's arguments filed 15 September 2003 and 24 September 2003 have been fully considered but they are not persuasive.

Applicant urges that the written description rejection is improper, given the description of the coding sequences, 5' and 3' regulatory regions of the genetic constructs. The Examiner maintains that the rejection was directed to the lack of an adequate written description of the broad genus of transcriptionally active, optionally non-conserved, intergenic spacer regions of the chloroplast genomes of a multitude plant species; given the description in the specification of only a single species of that genus, namely the trnI/trnA intergenic spacer. No guidance has been provided by the specification or any of Applicant's cited references regarding any sequences which are conserved between or diagnostic for transcriptionally active intergenic spacer regions of the chloroplast genome, as required by MPEP 2163, the case law cited by the Examiner, and the Written Description Guidelines.

Claims 3, 171 and 190-191 remain, and newly amended claim 214 is rejected under 35 U.S.C. 102(b) as being anticipated by Staub et al (1995), as stated on page 7 of the last Office action for claims 3, 171 and 190-191.

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Applicant's arguments filed 15 September 2003 and 24 September 2003 have been fully considered but they are not persuasive. Applicant urges that the prior art does not teach a universal vector because the *accD* gene is not universally present next to the *rbcL* gene in the chloroplast genome. The Examiner maintains that the amended claims no longer recite that the vector is "universal" or integrated into a *conserved* intergenic spacer region of the chloroplast genome. Additionally, the reference teaches that the *uidA* coding sequence of interest may lack a 5' promoter (see, e.g., page 846, Figure 1).

Claims 3-84, 86-96, 107, 118-119, 122, 168-169, 172-176, 189 and 193-196 are free of the prior art, as stated in the last Office action on page 7 for claims 4-84, 86-96, 107, 118-119, 122, 168-169, 172-176, 189, 193-199 and 214.

Claims 4-84, 86-96, 107, 118-119, 122, 168-169, 172-176, 189 and 194-195 remain allowed, as stated on page 7 of the last Office action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David T. Fox whose telephone number is (703) 308-0280. The examiner can normally be reached on Monday through Friday from 10:30AM to 7:00PM.

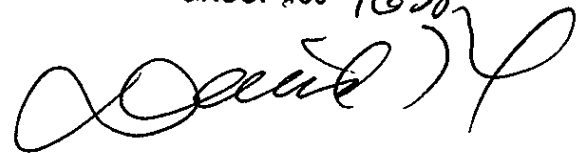
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (703) 306-3218. The fax phone number for this Group is (703) 872-9306. The after final fax phone number is (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December 15, 2003

DAVID T. FOX  
PRIMARY EXAMINER

GROUP 180 1638

A handwritten signature in black ink, appearing to read 'David T. Fox', is written over the printed name and title.